A Review of Eosinophilic Gastroenteritis

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Eosinophilic gastroenteritis (EG) is a rare disease of unknown etiology characterized by patchy or diffuse eosinophilic infiltration of the gastrointestinal tract wall with various gastrointestinal manifestations. As clinical presentation and radiological findings in EG are nonspecific, diagnosis requires a high index of suspicion and exclusion of other disorders that are associated with peripheral eosinophilia. This article reviews the history, current concepts of this complex disorder and the common symptoms. Because there is no gold standard for this disease, a wide variety of diagnostic criteria is presented.

Key words: eosinophilic gastroenteritis ■ eosinophilia ■ hypersensitivity reaction ■ immunoglobulin E ■ interleukin 5 ■ Tc-99m hexamethylpropyleneamineoxime

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BACKGROUND

Eosinophilic gastroenteritis (EG) is a rare and heterogeneous gastrointestinal disorder affecting both children and adults. It can present with various gastrointestinal manifestations, depending on the site of affected gastrointestinal tract and the layer of the gastrointestinal wall involved.[1,2] Definitive diagnoses requires histological demonstrations of eosinophilic infiltration of the gastrointestinal wall or high eosinophil count in ascitic fluid, absence of extra gastrointestinal eosinophilic infiltration and exclusion of other diseases that can present in similar fashion.

HISTORICAL PERSPECTIVE

This disorder was originally described in 1937 by Kaijser.[1] Subsequently, Klein et al. added seven new patients and conducted a review of the literature up to 1970. They defined three patterns of disease manifestation based on the initial symptoms. They related the clinical manifestations to the area of maximal gastrointestinal involvement and the depth of the disease process. The three main patterns were predominant mucosal layer disease, predominant muscle layer disease and predominant subserosal disease.[3]

In 1984, Oyaizu et al. presented evidence for the hypothetical IgE-induced, mast cell-mediated mechanism of eosinophilic chemotaxis in patients with EG.[4]

In 1990, Talley et al. categorized 40 patients with eosinophilic gastroenteritis according to the classification established by Klein et al.[2]

PATHOGENESIS

The underlying molecular mechanisms predisposing to this disease are unknown. The pathogenesis and etiology of the disease are not well understood, but many patients have history of seasonal allergies, food sensitivities, eczema, asthma, atopy and elevated serum IGE levels, suggesting that the hypersensitivity response plays a major role in pathogenesis.[5,6] Recent studies strongly support a role for eosinophils, Th-2 cytokines (IL-3, IL-5 and IL-13) and chemokines such as eotaxin (eosinophil selective chemokine) as the most critical factors in the pathogenesis of eosinophilic gastroenteritis and their intimate association with allergies and asthma. An imbalance in the T-cell paradigm causing an increase in the production of these cytokines has been postulated as the cause of IgE synthesis and eosinophilia.[7-9]

However, few studies suggest that the finding of extracellular major basic protein deposition in the intestinal mucosa of patients with EG is suggestive that the release of eosinophil granule proteins plays some role in the pathogenesis of EG.[3,10]

EPIDEMIOLOGY

The disease is rare, and the incidence is difficult to estimate. However, >280 cases have been reported in medical literature since the initial description of this disease by Kaijser.[1,5,8]

The majority of the cases of EG are reported in whites, with some cases occurring in Asians. A slight male preponderance has been reported. The majority of patients clinically present in the third-to-fifth decades, but the disease can affect any age group.[1-4]

CLINICAL FEATURES

EG manifests with an immense variety of chronic and often debilitating gastrointestinal symptoms depending on the site and the layer of the gastrointestinal tract involved. Mucosal EG, which is the most common EG subtype (25–100%), presents with fecal blood loss, anemia and weight loss secondary to malabsorption or protein losing enteropathy.[11] Muscularis EG (13–70% of all EG subtypes) often manifests as gastric outlet or small-bowel obstruction.[12] Subserosal EG (12–40%) manifests as eosinophilic ascites.[12]

EG can also present as obstructive jaundice and has the ability to mimic surgical conditions such as appendicitis and pancreatic cancer.[13-16]

Extraintestinal manifestations such as eosinophilic cystitis, eosinophilic splenitis and hepatitis have been described as well.[17,18]

DIAGNOSIS

Diagnostic evaluation of eosinophilic gastroenteritis is based on a high index of clinical suspicion. It is undertaken to exclude other diagnoses, establish the definitive diagnosis and to assess the complications associated with this disease.

Definitive diagnosis requires histological evidence of eosinophilic infiltration. As eosinophilic infiltrates can be diffused or patchy in distribution, multiple biopsies should be done to avoid missing the diagnosis. In patients with subserosal disease, abdominal paracentesis demonstrates a sterile fluid with a high eosinophil count.

Few studies also suggested the role of Tc-99m hexamethylpropyleneamineoxime (Tc-99m HMPAO)-labeled white blood cell (WBC) scintigraphy as a useful tool for detection of active eosinophilic infiltration in EG, but it does not help differentiating it from other causes of inflammation.[19-21] Peripheral eosinophilia is commonly found, but its presence as a diagnostic criterion is uncertain.

The absence of parasitic infestation or other extraintestinal diseases associated with eosinophilia are commonly mentioned but are not universally accepted as necessary diagnostic criteria.[22]

Differential Diagnosis

Diseases in which gastrointestinal symptoms are associated with peripheral eosinophilia should be differentiated from EG. Usually these diseases can easily be distinguished from EG with simple laboratory tests or biopsies.

Some of the major diseases that can mimic EG and should be differentiated are: intestinal parasites such as Ascaris, Anisakis, Ancylostoma, Strongyloides, Capillaria, Toxicara, Trichiura and Trichinella. All cause eosinophilia and can be excluded with careful examination of the stool for ova or parasites.[23-27]

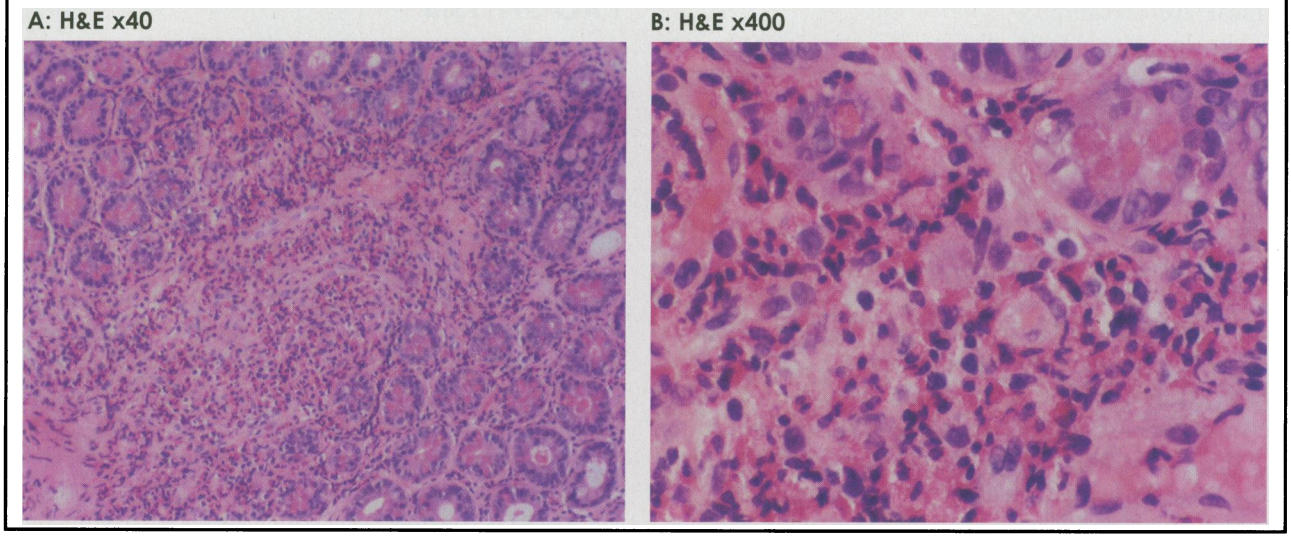
Rarely, Crohn's colitis or ulcerative colitis might be associated with peripheral eosinophilia, but these diseases can usually be excluded by biopsy because these diseases lack florid eosinophilia.[28]

Hypereosinophilia syndrome (HES) is an idiopathic condition associated with gastroenteritis and marked peripheral eosinophilia exceeding 1,500 cells/μl for >6 consecutive months. Major targets of HES are heart, lungs, and the brain and kidneys, with >55% of patients presenting with a complication in ≥1 of these sites.[29]

Endoscopic Appearance

The gross appearance of EG shows erythematous, nodular, friable and often ulcerated mucosa. Diffuse enteritis with complete loss of villi, infiltration of the gastrointestinal wall, submucosal edema and fibrosis may be present.[2,22,30,31]

Figure 1. Small-bowel mucosa with normal villous pattern and patchy intense sheet-like infiltrate of eosinophils in the lamina propria



Role of Biopsy

The diagnosis of EG is confirmed by biopsies that reveal >20 eosinophils per high-power field on microscopic examination.[2,32,33] Upper gastrointestinal endoscopy with biopsy of the stomach and small intestine is diagnostic in up to 80% of patients.[2,31] However, biopsies from both normal and abnormal appearing mucosa should be taken because even the normal appearing mucosa can harbor the diagnostic microscopic appearance.[33] Biopsies revealing increased eosinophils in sheets along with mucosal architectural abnormalities (loss of normal features) are diagnostic in the appropriate clinical setting. On the other hand, even multiple normal mucosal biopsies cannot exclude the diagnosis of eosinophilic gastroenteritis, given its patchy mucosal involvement in some patients.[10,31]

Role of Imaging Studies

Radiographically, EG does not have a pathognomonic appearance. Radiographic changes are variable, nonspecific, and/or absent in at least 40% of patients.

Ultrasound and computed tomography scans may show thickened intestinal walls and, occasionally, localized lymphadenopathy. However, similar changes can also be found in other diseases such as Crohn's disease, lymphoma and granulomatous disease.[34-35]

Role and Usefulness of Tc-99m HMPAO Scan

Recently, few studies and case reports have suggested the role of the Tc-99m HMPAO scan in detection of active inflammation in EG. In one study by Lee et al., it has been reported to be useful in assessing the extent of disease and response to treatment.[19]

HISTOLOGIC FINDINGS

Histopathology usually demonstrates increased numbers of eosinophils (>20 eosinophils per high-power field) in the lamina propria. Large numbers of eosinophils are often present in the muscularis and serosal layers (Figure 1).

The localized eosinophilic infiltrates may cause crypt hyperplasia, epithelial cell necrosis and villous atrophy. Mast-cell infiltrates and hyperplastic mesenteric lymph nodes infiltrated with eosinophils may be present.[2,10,31-33]

TREATMENT

There have been no randomized prospective clinical trials regarding therapy. Thus, the treatment is empirical and based on the severity of the clinical manifestations. Patients with mild disease can be treated symptomatically.[33] More symptomatic patients and those with evidence of malabsorption need more aggressive therapy.

The role of an elimination diet is controversial. Retrospective studies indicate that an elimination diet can lead to clinical and histological improvement in EG, but all of these involve the use of dietary therapy in combination with other interventions.[12]

Corticosteroid therapy is the mainstay of treatment of EG both in adults as well as in children. The appropriate duration of steroid therapy is unknown. Daily administration of prednisone is recommended, and improvement usually occurs within two weeks regardless of the site and layer of the bowel involved.[22,32]

The subsequent course is quite variable. Some patients have no recurrences, while a few experience recurrent symptoms during or immediately after the prednisone taper. The latter patients may require long-term, low-dose maintenance therapy with prednisone (e.g., 5–10 mg/day).[3,32] Other patients experience periodic flares months to years after the initial episode. They can be well managed with another short course of oral prednisone, 20–40 mg/day, followed by a rapid taper.[32]

Other medications, including sodium cromoglycate and ketotifen (antihistamine and mast-cell stabilizing agents), budesonide and suplatast tosilate (antiallergic drug that suppresses cytokines production), were found to be effective in the management as well as steroid-sparing agents in some case reports but not in the others.[36-41]

There are few reports and small studies about the use of montelukast (selective leukotriene receptor antagonist) both in adults and children showing promising results. However, a large randomized trial is required.[40,42] Results of one small study evaluating the efficacy and safety of a humanized anti-interleukin-5 antibody in patients' refractory to other treatments is quite encouraging. Preliminary results showed reduction in peripheral and tissue eosinophil counts and improved quality of life. However, larger randomized, controlled trials are needed to confirm these results.[43,44]

Surgical treatment is only required for patients with intestinal perforation and/or obstruction or when performing a full-thickness intestinal biopsy to establish the diagnosis.

PROGNOSIS

Untreated patients with EG can progress to severe malabsorption and malnutrition or remit spontaneously. However, the long-term prognosis for this condition is good.[3,33]

FUTURE PERSPECTIVE

Currently, there are a few novel and emerging treatment agents under investigation. These include eosinophil selective adhesion molecules, a monoclonal eotaxin antibody (CAT-213) and agents to enhance eosinophil apoptosis. Hopefully, these emerging therapies will not only be more effective but also safely used.[45]

CONCLUSION

EG is a rare disease that is being increasingly recognized as a primary process associated with allergies. It should be suspected in patients having gastrointestinal

discomfort along with peripheral eosinophilia and where standard examinations could not give the explanation. Early diagnosis enables successful treatment, and decreases unnecessary surgical operations and mortality.

Histopathologic findings of eosinophilic infiltration are required to confirm the diagnosis due to the nonspecific clinical presentations. Hopefully, future advances will enable us to develop a noninvasive and reliable follow-up.

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